

Oral Immune-Related Adverse Events – Current Concepts and their Management

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ABSTRACT

Recent advent of immune checkpoint inhibitors (ICIs) have made significant improvement in the treatment outcome of cancer patients. They are also known to increase the overall survival in many malignancies. They target key immune checkpoints, acting on the cytotoxic T-lymphocyte antigen-4, programmed death-1 (PD-1), and PD-1 ligand 1 pathways. ICIs are effective in cancer therapy, but also possess various adverse effects that are termed together as immune-related adverse events (irAEs). Information focusing only on the oral reactions of irAEs is scanty

in the literature. Therefore, we performed a computerized database search in PubMed and Google Scholar to identify and collect data regarding the oral adverse effects of ICIs. The early recognition of oral irAEs and appropriate intervention may help in improving the quality of life in patients. This paper presents a brief review of oral irAEs and their management.

Key words: Immune-related adverse events, immunotherapy, oral mucositis, quality of life

Introduction

Recent developments in oncology have led to newer insights in understanding the molecular carcinogenesis and enabled the adoption of newer therapeutic strategies. Immune checkpoint inhibitors (ICIs) are one among those recent advancements that has brought drastic improvement in the outcome of cancer therapy. These inhibitors act on cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), and PD-1 ligand 1 (PD-L1) pathways targeting the immune checkpoints.^[1,2] These antibodies are known to give promising results in various cancers including melanoma, head-and-neck cancers, renal cell carcinoma, non-small-cell lung cancer, and other solid

tumors.^[3] They act by hindering the inhibitory pathway between T-lymphocytes and tumor cells. They also induce reactivation of T-cells and anti-tumor cytolytic activities.^[2] ICIs that are approved by Food and Drug Administration include ipilimumab (anti-CTLA-4), pembrolizumab and nivolumab (PD-1 inhibitors), atezolizumab, durvalumab, and avelumab (PD-L1 inhibitors).^[4] Though ICIs are effective in improving the clinical outcome, they are also accompanied with various adverse effects that are grouped together as immune-related adverse events (irAEs).^[5] Oral reactions of irAEs are very common, but literature focusing only on the oral irAEs is scanty. Therefore, we performed

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a computerized database search in PubMed and Google Scholar to identify and collect data regarding the oral adverse effects of ICIs. Here, in this paper, we present a brief review of oral irAEs and their management.

Immune-Related Adverse Events

irAEs is an extensive term that includes a set of side effects related to ICI and their autoimmune reactions. irAEs can affect multiple organ systems including skin, gastrointestinal (GI) tract, pulmonary, endocrine, musculoskeletal, and other systems. They can also cause severe pneumonitis and myocarditis that can be fatal.^[6] Skin, gastrointestinal tract including oral mucosal and hepatic reactions, endocrine and pulmonary reactions are the most frequently encountered irAEs. Oral reactions are known to exist along with dermatological and GI reactions.^[7] irAEs are considered as immune reactions owing to the reactivated T cells. These reinvigorated T-cells exert some amount of devastating effect to the normal cells and tissues apart from acting against the tumor cells.^[3] The incidence and severity of irAEs vary based on the ICI used. According to literature evidences, irAEs have been reported in up to 70% cases on CTLA-4 inhibitor therapy and 30% have been reported with PD-1 inhibitor therapy.^[8] Combination therapy with these inhibitors has shown to cause severe irAEs.^[9] Colitis is encountered frequently in patients treated with ipilimumab, whereas in patients treated with nivolumab or pembrolizumab, pneumonitis is common.^[6] Various oral adverse reactions, especially mucositis, are frequently reported in patients undergoing PD-1 inhibitor therapy.^[10] Majority of the irAEs are mild and reversible immune reactions, but sometimes, they can progress to fatal conditions. These adverse reactions have major clinical implications. They require multidisciplinary approach and may demand discontinuation and dose alteration of ICI for the management.^[11,12] According to the observations of Shah *et al.*, an incidence of about 55.2% of xerostomia, 33.6% of oral mucositis (OM), and 11.2% of lichenoid reactions was reported in patients treated with ICI therapy.^[13]

Oral Mucositis

The inflammation of oral mucosa that occurs due to cancer therapy is known as OM. It manifests as swelling, atrophy, erythema, and ulcerations of the oral mucosa.^[14] OM is known to be a frequent oral irAEs of anti-PD-1 inhibitors than CTLA-4 inhibitors. Incidence of up to 2% has been reported in the treatment of metastatic or recurrent head-and-neck squamous cell carcinomas with nivolumab and pembrolizumab. Most cases of OM reported in the literature were of Grades 1 and 2.^[15] According to literature

evidence, pembrolizumab-induced OM is rare and it is known to appear around 11–14 months from the initiation of therapy,^[16] but Yoon *et al.* have reported a case of severe OM presenting as multiple and extensive ulcerations of the oral mucosa and lips, followed by pembrolizumab therapy for SCC of lungs within 3 months from the start of the therapy.^[17] Pathogenesis of OM due to ICI is believed to be the same as that of conventional chemotherapy-induced OM. The ICI or chemotherapeutic agent initiates the pathogenic events by causing the release of reactive oxygen species and damage to the DNA. This affects the suprabasal and basal cells of the epithelium resulting in apoptosis and release of specific protein molecules. Once this initiation process is completed, a series of enzyme-mediated events takes place resulting in the activation of transcription factors leading to the upregulation of genes and releases of pro-inflammatory cytokines. These cytokines cause further damage to the epithelial cells and fibroblasts. The affected fibroblasts induce the secretion of matrix metalloproteinases (MMP), such as MMP1 and MMP3 causing destruction of the epithelial basement membrane. They also cause damage to the keratinocytes that promote the release of transforming growth factor-beta 1 and inhibit the cell cycle. All these sets of events constitute the second and third stages of mucositis development. The fourth stage is where the integrity of the mucosa and submucosa is disrupted resulting in ulceration. The oral microflora also gets altered owing to these mucosal changes and contributes to the promotion of mucositis. This process of damage to the oral mucosa continues by the active production of inflammatory cytokines until the end of treatment or withdrawal of the anticancer agent. After the withdrawal or end of the cancer therapy, the final stage of healing takes place by promotion of re-epithelization.^[18,19]

Clinically, OM may present as diffuse erythema with ulcerations of the oral mucosa. The ulcerative lesions of mucositis can be differentiated from aphthous stomatitis by the absence of a peripheral erythematous ring [Figure 1]. According to the World Health Organization, OM is classified based on the signs and symptoms [Table 1]

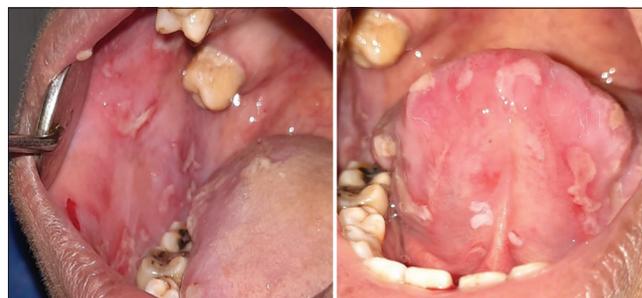


Figure 1: Multiple oral ulcerations with pseudomembranous slough secondary to pembrolizumab therapy for lung cancer

ranging from mild to severe.^[20,21] The symptoms reported by the patients are pain, difficulty in swallowing and speech depending on the severity of mucositis.^[22] According to Mucositis study group of the multinational association of supportive care in cancer/International Society of Oral Oncology (MASCC/ISOO) guidelines for the prevention of chemotherapy-induced OM, oral cryotherapy for a period of 20–30 min, before the induction of the therapy can help in preventing OM.^[23] Management of OM includes topical corticosteroids and analgesics. Topical antifungals are prescribed sometimes to reduce the oral microbial load and secondary fungal infections. Transdermal fentanyl is used in case of chemotherapy-induced OM for pain alleviation.^[21,24] Antimicrobial doses of doxycycline (100 mg/day) were also used in cases of ICI-induced OM along with corticosteroid therapy.^[13] Photobiomodulation using low-level lasers is an effective treatment modality for the management of OM. Studies have shown that laser therapy can prevent mucositis and also reduce the risk of developing severe mucositis up to 62% in patients receiving chemo and radiotherapy. According to the literature evidence, 670–830 nm of gallium–aluminum–arsenide lasers (GaAlAs), 660 nm of indium–gallium–aluminum phosphide lasers (InGaAlP), and diode lasers operating at 940 nm were proven to be effective in the management of OM.^[25,26] Jacob *et al.* studied the clinical characteristics and outcome of gastrointestinal mucositis including OM, associated with ICI therapy. They reported that most of the cases were mild, about 25% of cases required intervention with immunosuppressants. Recurrence was reported in about 38% of cases.^[27] However, there are no standardized treatment protocols for the management of ICI-induced OM.

Xerostomia

Subjective feeling of dryness of the oral cavity because of reduced salivation is termed xerostomia. In a normal healthy adult, the average stimulated salivary flow rate is about 1.5–2.0 mL/min and the unstimulated salivary flow rate is about 0.3–0.4 mL/min. In case of xerostomia, the stimulated salivary flow rate is reduced below 0.5 mL/min.^[28] Xerostomia is a major side effect of cancer radio and chemotherapy. It is also reported to be a chronic irAEs that occurs within 2–8 months in patients treated with ICIs. Xerostomia has been reported in patients treated with nivolumab and pembrolizumab. Features of xerostomia may mimic Sjogren's syndrome, but they do not show positivity to anti-SSA and SSB antibodies.^[29,30] Takahashi *et al.* have reported sialadenitis and xerostomia in a patient treated with nivolumab for adenocarcinoma of lung.^[31] Katsura *et al.* hypothesized that xerostomia associated with ICI therapy is caused by damage to the salivary acini due to lymphocytic

infiltration induced by ICI therapy.^[32] Warner *et al.* also reported diffuse T-lymphocytic infiltration in minor salivary glands in cases of ICI-induced xerostomia.^[33]

Management of xerostomia includes topical oral lubricants, saliva stimulants, and substitutes. Pilocarpine and cevimeline are potent salivary stimulators that act on muscarinic receptors. Five milligram of pilocarpine or 30 mg of cevimeline thrice daily for at least 3 months is used for effective management of xerostomia. Oral lozenges of anhydrous crystalline maltose have been shown to stimulate saliva production. Topical application of physostigmine on the oral mucosa is known to act on the minor salivary glands and increase the saliva production.^[28] Amifostine is also beneficial in the management of OM and xerostomia among patients undergoing radio and chemotherapy.^[34] Electrostimulation and photobiomodulation with low-level lasers are proven to be effective methods of stimulating the salivary production and flow.^[35,36] Extraoral application of low-level lasers on the region of major salivary glands promotes salivary stimulation and regeneration of the salivary acini.^[37] Xerostomia can lead to progression of dental caries and periodontal diseases; hence, routine oral health checkup is mandatory in these patients.

Dysgeusia

Dysgeusia is a diminished or unpleasant alteration in the taste sensation. Dysgeusia is a common side effect of radio and chemotherapy that can exert a direct negative impact on their quality of life.^[38] According to the Common Terminology Criteria for Adverse Events, dysgeusia can be classified into two grades [Table 2]. Dysgeusia has been reported in <3% of patients undergoing PD-1 and PD-L1 inhibitors therapy, but it is uncommon in patients treated with anti-CTLA-4 agent.^[29,39] These drugs can cause cell damage, alteration in the cell surface receptors, and interruption in the neural coding of taste buds leading to impaired taste

Table 1: Grading of oral mucositis

Grade	Clinical features
0 (none)	No changes
I (mild)	Pain and erythema of the oral mucosa
II (moderate)	Oral mucosal ulcers and erythema. A patient can tolerate solid food
III (severe)	Extensive oral ulcers. A patient can tolerate only liquid diet
IV (life threatening)	Oral alimentation will not be possible

Table 2: Grading of dysgeusia

Grade	Clinical features
I	Alteration in taste sensation but no change in diet
II	Alteration in taste with change in diet, noxious or unpleasant taste, loss of taste

sensation. Oral zinc supplements including zinc gluconate can help in regulation of pores of the taste buds. Amifostine is also used in the prevention of dysgeusia.^[40] Low-level laser therapy using a diode laser for irradiation of several areas of the dorsum of the tongue has been shown to improve the taste perception.^[41] Cecchi *et al.* have reported a case of black hairy tongue associated with burning sensation and dysgeusia after pembrolizumab therapy for advanced lung cancer. The tongue features have persisted for a longer time even after discontinuation of the therapy. Black hairy tongue is considered as an atypical oral irAEs.^[42]

Lichenoid Reactions

Treatment with PD-1 and PD-L1 inhibitors is known to cause lichenoid lesions with involvement of various intraoral sites.^[43] These lesions show clinical and histological consistency with oral lichenoid lesions. The common site of involvement includes lateral borders and dorsum of tongue, buccal, labial, and palatal mucosa. These lesions usually occur months after the induction of ICI therapy. They appear as whitish patches or papules with irregular borders [Figure 2]. Sometimes, they appear erythematous and ulcerative. The presence of linear streaks or striae may be prominent along the borders of the lesion. Patients may experience pain and burning sensation, occasionally they can be asymptomatic. Apart from the oral involvement, skin, vulva, or the perianal area can also be affected.^[43,44] Shazib *et al.* reported a series of cases with lichenoid lesions followed by PD-1 inhibitor therapy. Few of those cases developed severe oral ulcerations that required discontinuation and alteration in the PD-1 inhibitor therapy.^[10] Dermal Lichenoid reactions without involvement of mucosal membranes are reported in about 25% of undergoing ICI therapy.^[45] Intraoral lesions can



Figure 2: Faint oral lichenoid lesion of the buccal mucosa associated with burning sensation secondary to pembrolizumab therapy for lung cancer

be managed with topical corticosteroids. But in case of extensive lesions with dermal involvement, systemic corticosteroids are considered.

Combined Oral and Dermal Lesions

ICI therapy is also known to cause Stevens–Johnson syndrome, bullous pemphigoid (BP), drug reactions manifesting with eosinophilia and systemic symptoms Nayar *et al.* have reported toxic epidermal necrolysis with intraoral involvement. Jour *et al.* have reported BP and Utsunomiya *et al.* have reported erythema multiforme. These dermal toxicities may present with intraoral ulcerations of various intraoral sites.^[46-48] Dermal toxicities are reported more frequently in patients undergoing combination therapy. BP involving both skin and oral mucosa has also been reported in the literature. ICI-related BP is usually eosinophil and mixed inflammatory infiltrates predominant.^[49] However, Morris *et al.* have reported a series of cases with ICI-related neutrophil predominant BP.^[50] Assessment of these toxicities should include for determination of the extent of involvement by a thorough examination of the skin including the mucosa, documentation of the toxicities after ruling out other possible etiologies, biopsy for histopathological examination, and devising a treatment plan. Toxicities of Grades 1 and 2 do not require alteration in the ICI therapy, but Grades 3 and 4 toxicities require alteration or discontinuation of the ICI therapy along with specialist consultation.^[10]

Conclusions

Treatment with ICIs has increased the treatment responses and survival benefit in cancer patients. However, the risk of irAEs in ICI use is a challenge to health-care professionals as they may require additional therapy, which increases the cost and length of hospitalization at times. Effects of Oral irAEs may be underestimated, but they can also affect nutrition and speech. Hence, awareness of the oral toxicities can aid in their early diagnosis and providing appropriate intervention which may improve the quality of life of the patients.

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Conflicts of interest

There are no conflicts of interest.

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